# VERIFICATION OF TRANSLATION

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Yosuke Hisamatsu

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[Filing Fee]

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[Title of Document] Description 1

[Title of Document] Drawings 1

[Title of Document] Abstract 1

[Title of Document] CLAIMS

[Claim 1]

The transdermal preparation for treating increased urinary frequency and urinary incontinence, containing as an active ingredient 4-(2-methyl-1-imidazolyl)-2,2-diphenylbutylamide and comprising an external preparation base and a structural body.

[Claim 2]

The transdermal preparation for treating increased urinary frequency and urinary incontinence according to claim 1, which is of a single adhesive layer type, comprising:

an adhesive layer formed of 4-(2-methyl-1-imidazolyl)-2,2-diphenylbutylamide in conjunction with a single or combination of the external preparation bases; and

a structural body comprising a support and a peelable liner.

[Claim 3]

The transdermal preparation for treating increased urinary frequency and urinary incontinence according to claim 1, which is of a reservoir type, comprising:

a mixture of 4-(2-methyl-1-imidazolyl)-2,2-diphenylbutylamide and a single or combination of the external preparation bases; and

a structural body comprising a membrane for controlling drug permeation, an adhesive layer, a support, and a peelable

liner.

[Claim 4]

The transdermal preparation for treating increased urinary frequency and urinary incontinence according to any one of claims 1 to 3, wherein the external preparation base comprises a compound or combination of compounds selected from the group consisting of a water-soluble polymer, a fat-soluble polymer, a fatty acid, a fatty acid ester, a fatty acid metal salt, animal or plant fats and oils, an alcohol, a terpene compound, and water.

[TITLE OF DOCUMENT] DESCRIPTION

[TITLE OF THE INVENTION] TRANSDERMAL PREPARATION FOR TREATING INCREASED URINARY FREQUENCY AND URINARY INCONTINENCE

[TECHNICAL FIELD]

[0001]

The present invention relates to a transdermal preparation containing as an active ingredient 4-(2-methyl-1-imidazolyl)-2,2-diphenylbutylamide (which is referred to as KRP-197, hereinafter), having a bladder-selective anticholinergic effect and used as a treatment for increased urinary frequency and urinary incontinence.

[BACKGROUND ART]

[0002]

KRP-197 is a novel selective muscarinic antagonist (Patent Document 1) and is considered a potential cure for increased urinary frequency and urinary incontinence (Non-Patent Document 1).

[0003]

Like other commercially available drugs for treating increased urinary frequency and urinary incontinence, KRP-197 is provided in the form of oral solid preparation (*i.e.*, tablets) (Patent Document 2).

[Patent Document 1] Japanese Patent Laid-Open Publication No. Hei 7-15943

[Patent Document 2] WO01/34147 A1 Pamphlet

[Non-Patent Document 1] Bioorg. Med. Chem., 1999, 7, 1151-1161.

[DISCLOSURE OF THE INVENTION]

[PROBLEMS TO BE SOLVED BY THE INVENTION]

[0004]

Recent advances in medicine have led to the emergence of an aging population and it is estimated that more people will suffer from increased urinary frequency and urinary incontinence and the type of the patients with these symptoms will be shifted in the future. As in KRP-197, more patient-oriented non-oral preparations are desired so as to improve the quality of lives of the patients to whom oral administration is hardly applied.

[0005]

Among possible forms of non-oral preparations are injections and external preparations (such as liquids, ointment and infusions). While having immediate pharmacological effects, injections require careful control of delivery methods and doses by medical personnel as compared to other preparations and are associated with burdensome problems such as difficulty in administering at home, accompanying pain and inability to eliminate drug that has once been administered. On the other hand, external preparations are less burdensome to patients as compared to the injections since the external preparations can be applied at home,

accompany no pain and can eliminate drug after application. Nonetheless, some drawbacks still remain: External preparations are generally applied by patients themselves or their caretakers, so that the poorly controlled drug delivery or dosage may lead to a reduced chance of proper drug use. Thus, injections and conventional external preparations are not sufficiently effective for use with patients of a wide age range and their caretakers.

[0006]

Recently, transdermal preparations that employ the concept of drug delivery system to achieve optimum treatment have attracted much attention and have been intensively studied. Such preparations have overcome the above-described drawbacks of conventional external preparations and, at the same time, offer sustained drug efficencies and reduced side effects, distinctive features that have never been achieved by conventional external preparations, along with the advantages of the conventional external preparations. Nevertheless, the barrier function of the skin reduces the drug absorption from the skin and often prevents delivery of effective doses of drugs by a patch with a practical surface area.

[0007]

Transdermal absorption of KRP-197 is significantly low when the drug is used alone in a transdermal preparation, and it has been considered difficult to achieve effective blood

concentrations of the drug.

[0008]

The present invention addresses the above-described problem, and it is thus an object of the present invention to provide an effective transdermal preparation that ensures stable and sustained absorption of KRP-197, into body while causing little skin irritancy.

[MEANS FOR SOLVING THE PROBLEMS]

[0009]

In an effort to achieve the aforementioned object, the present inventors have discovered that a single adhesive layer-type transdermal preparation or a reservoir-type transdermal preparation obtained by depositing a mixture of KRP-197 and an external preparation base onto a structural body can ensure high permeation of KRP-197 through the skin and sustained absorption of KRP-197 into body while causing decreased skin irritancy. The mixture is deposited onto the structural body by spreading it over the structural body and drying it or by depositing a small pool of the mixture on the structural body.

[0010]

Accordingly, the present invention concerns the following:

(1) The transdermal preparation for treating increased urinary frequency and urinary incontinence, containing as an

active ingredient KRP-197 and comprising an external preparation base and a structural body;

(2) The transdermal preparation for treating increased urinary frequency and urinary incontinence according to (1) above, which is of a single adhesive layer type, comprising:

an adhesive layer formed of KRP-197 in conjunction with a single or combination of the external preparation bases; and

a structural body comprising a support and a peelable liner;

(3) The transdermal preparation for treating increased urinary frequency and urinary incontinence according to (1) above, which is of a reservoir type, comprising:

a mixture of KRP-197 and a single or combination of the external preparation bases; and

a structural body comprising a membrane for controlling drug permeation, an adhesive layer, a support, and a peelable liner; and

(4) The transdermal preparation for treating increased urinary frequency and urinary incontinence according to any one of (1) to (3) above, wherein the external preparation base comprises a compound or combination of compounds selected from the group consisting of a water-soluble polymer, a fat-soluble polymer, a fatty acid, a fatty acid ester, a fatty acid metal salt, animal or plant fats and oils, an alcohol, a terpene compound, and water.

[ADVANTAGE OF THE INVENTION]

[0011]

Although KRP-197 which is used as a treatment for increased urinary frequency and urinary incontinence are hardly absorbed through the skin, the transdermal preparation for treating increased urinary frequency and urinary incontinence provided in accordance with the present invention ensures stable, effective and sustained absorption of KRP-197, into body while being less irritant to the skin.

[0012]

The active ingredient of the transdermal preparation of the present invention, KRP-197 may be used either as a free form or as a medically acceptable salt.

[BEST MODE FOR CARRYING OUT THE INVENTION]

[0013]

4-(2-methyl-1-imidazolyl)-2,2-diphenylbutylamide, or KRP-197, the active ingredient of transdermal preparation for treating increased urinary frequency and urinary incontinence of the present invention, has a bladder-selective anticholinergic effect and can be used as a treatment for increased urinary frequency and urinary incontinence.

[0014]

While the external preparation base for use in the transdermal preparation of the present invention may be any base commonly used in external preparations, it is preferably

a water-soluble polymer (*e.g.*, polyacrylic acids and derivatives thereof, cellulose derivatives, polyvinyl alcohols, gelatin, poloethylene glycol, and naturally-occurring polysaccharides), fat-soluble polymers (*e.g.*, natural rubbers, isoprene rubber, butyl rubber, styrene-isobutylene block copolymers, styrene-butadiene copolymers, silicone, lanoline, vaseline, plastibase, beeswax, cetaceum, and solid paraffin), fatty acids and derivatives thereof (*e.g.*, fatty acid esters and metal salts thereof), animal and plant fats and oils (*e.g.*, olive oil, mint oil, soybean oil, cottonseed oil, corn oil, eucalyptus oil, castor oil and sesame oil), alcohols (ethanol, glycerol, propylene glycol and polyethylene glycol), terpene compounds (menthol, menthone, limonene, pinene, piperitone, teripinene, terpinolene, terpinol, and carveol) and water. These external preparation bases may be used either individually or in combination.

[0015]

The transdermal therapeutic preparation for treating increased urinary frequency and urinary incontinence of the single adhesive layer type provided in accordance with the present invention according to claim 2(referred to as "single adhesive layer-type transdermal preparation," hereinafter) consists of an adhesive layer and a structural body consisting of a support and a peelable liner for protecting the adhesive layer. The adhesive layer contains the active ingredient KRP-

197 and is formed of a base or combination of bases selected from the above-described external preparation bases. One embodiment of the single adhesive layer-type transdermal preparation is shown in cross-section in Fig. 1.

[0016]

While the support for forming the structural body of the single adhesive layer-type transdermal preparation may be any suitable support, it is preferably flexible enough to not cause significant discomfort when applied to the skin surface. Such a support may be a single-layer or multilayer film formed of materials including plastic films (*e.g.*, polyethylene, polypropylene, polyester, poly vinyl acetate, and ethylene-vinylacetate copolymer), metal foils (*e.g.*, aluminum foil), nonwoven fabric, fabric and paper. While the peelable liner may be any suitable liner, it is preferably a paper strip or plastic film treated with a silicone resin or fluorine resin to make it peelable.

[0017]

The reservoir-type transdermal preparation for treating increased urinary frequency and urinary incontinence of the present invention according to claim 3 comprises a mixture of the active ingredient KRP-197 and a base or combination of bases selected from the above-described external preparation bases (reservoir content); and a structural body comprising a membrane for controlling drug permeation, an adhesive layer, a

support that can hold the reservoir content, and a peelable liner. One embodiment of the reservoir-type therapeutic transdermal preparation for treating increased urinary frequency and urinary incontinence is shown in cross-section in Fig. 2.

[0018]

While the support for forming the structural body of the reservoir-type may be any suitable support that can hold the reservoir content, supports similar to those used in the single adhesive layer-type transdermal preparations may be used. While the peelable liner may be any suitable liner, liners similar to those used in the single adhesive layer-type transdermal preparations may be used. The drug permeability control membrane may be a fine porous membrane, such as fine porous polypropylene, or other membrane materials that can control the drug permeability. The adhesive layer may be formed of a rubber-based, acryl-based or silicone-based tackifier that is permeable to the drug. It may be a double-sided tape. The adhesive layer may also serve as the drug permeability control membrane.

[0019]

The present invention will now be described in detail with reference to examples, which are not intended to limit the scope of the invention in any way.

[0020]

Examples of single adhesive layer-type transdermal preparation are presented in Examples 1 through 4, and examples of reservoir-type transdermal preparation are presented in Examples 5 and 6.

[Example 1]

[0021]

0.1 parts by weight of KRP-197 were dissolved in 37.5 parts by weight of chloroform. To this solution, 3.95 parts by weight of styrene-isobutylene-styrene block copolymer (Trade name Kraton D1107CU, Kraton Polymers Japan Co., Ltd.), 4.95 parts by weight of a ultra-pale rosin ester (Trade name Ultra pale rosin ester KE-311, Arakawa Chemical Co., Ltd.) and 1 part by weight of isopropyl myristate were added, and the mixture was stirred to dissolve the components. This gave an adhesive layer. Using a Baker applicator with a thickness setting of 10 scales, the resulting adhesive layer was spread over a support (Trade name 3M Scotchpak 9742 Release Liner, Sumitomo 3M Co., Ltd.) on its polyester surface. Three strips of double-sided tape were stuck to each leg of the applicator. The coated support was dried at room temperature for about 15min and was further dried in a drier at 60°C for about 15min. The adhesive surface was then laminated with a peelable liner (Trade name 3M Scotchpak 9742 Release Liner, Sumitomo 3M Co., Ltd.) with its fluorine polymer surface facing the adhesive layer. This gave a single adhesive layer-type transdermal

preparation.

[Example 2]

[0022]

0.1 parts by weight of KRP-197 were dissolved in 37.5 parts by weight of chloroform. To this solution, 2.85 parts by weight of styrene-isobutylene-styrene block copolymer (Trade name Kraton D1107CU, Kraton Polymers Japan Co., Ltd.), 5.05 parts by weight of a ultra-pale rosin ester (Trade name Ultra pale rosin ester KE-311, Arakawa Chemical Co., Ltd.), 1 part by weight of isopropyl myristate and 1 part by weight of liquid paraffin were added, and the mixture was stirred to dissolve the components. This gave an adhesive layer. Using a Baker applicator with a thickness setting of 10 scales, the resulting adhesive layer was spread over a support (Trade name 3M Scotchpak 9742 Release Liner, Sumitomo 3M Co., Ltd.) on its polyester surface. Three strips of double-sided tape were stuck to each leg of the applicator. The coated support was dried at room temperature for about 15min and was further dried in a drier at 60°C for about 15min. The adhesive surface was then laminated with a peelable liner (Trade name 3M Scotchpak 9742 Release Liner, Sumitomo 3M Co., Ltd.) with its fluorine polymer surface facing the adhesive layer. This gave a, single adhesive layer-type transdermal preparation.

[Example 3]

[0023]

0.1 parts by weight of KRP-197 were dissolved in 37.5 parts by weight of chloroform. To this solution, 3.95 parts by weight of styrene-isobutylene-styrene block copolymer (Trade name Kraton D1107CU, Kraton Polymers Japan Co., Ltd.), 4.95 parts by weight of a ultra-pale rosin ester (Trade name Ultra pale rosin ester KE-311, Arakawa Chemical Co., Ltd.) and 1 part by weight of oleyl alcohol were added, and the mixture was stirred to dissolve the components. This gave an adhesive layer. Using a Baker applicator with a thickness setting of 10 scales, the resulting adhesive layer was spread over a support (Trade name 3M Scotchpak 9742 Release Liner, Sumitomo 3M Co., Ltd.) on its polyester surface. Three strips of double-sided tape were stuck to each leg of the applicator. The coated support was dried at room temperature for about 15min and was further dried in a drier at 60°C for about 15min. The adhesive surface was then laminated with a peelable liner (Trade name 3M Scotchpak 9742 Release Liner, Sumitomo 3M Co., Ltd.) with its fluorine polymer surface facing the adhesive layer. This gave a single adhesive layer-type transdermal preparation.

[Example 4]

[0024]

0.1 parts by weight of KRP-197 were dissolved in 37.5 parts by weight of chloroform. To this solution, 3.95 parts by weight of styrene-isobutylene-styrene block copolymer (Trade name Kraton D1107CU, Kraton Polymers Japan Co., Ltd.), 4.9

parts by weight of a ultra-pale rosin ester (Trade name Ultra pale rosin ester KE-311, Arakawa Chemical Co., Ltd.), 1 part by weight of olive oil and 0.5 parts by weight of L-menthol were added, and the mixture was stirred to dissolve the components. This gave an adhesive layer. Using a Baker applicator with a thickness setting of 10 scales, the resulting adhesive layer was spread over a support (Trade name 3M Scotchpak 9742 Release Liner, Sumitomo 3M Co., Ltd.) on its polyester surface. Three strips of double-sided tape were stuck to each leg of the applicator. The coated support was dried at room temperature for about 15min and was further dried in a drier at 60°C for about 15min. The adhesive surface was then laminated with a peelable liner (Trade name 3M Scotchpak 9742 Release Liner, Sumitomo 3M Co., Ltd.) with its fluorine polymer surface facing the adhesive layer. This gave a single adhesive layer-type transdermal preparation.

[Example 5]

[0025]

0.2 parts by weight of KRP-197 were dispersed in 0.05 parts by weight of L-menthol in 9.75 parts by weight of an ethanol(99.5)/water mixture (mass ratio = 1 : 1.3) to give a KRP-197 dispersion. A double-sided tape (Trade name Double-sided paper adhesion tape, Kokuyo Co., Ltd.) was used as the drug permeability control membrane.

[Example 6]

[0026]

To 0.2 parts by weight of KRP-197, 0.05 parts by weight of L-menthol, 0.2 parts by weight of HPCM, and 9.75 parts by weight of an ethanol(99.5)/water mixture (mass ratio = 1 : 1.3) were added and the components were dispersed to give a material to serve as the reservoir content. 0.9 g of this material were stuffed in a support (Trade name Cosmopack PTP, Kanae Co., Ltd.) and the opening of the support was sealed with a strip of double-sided tape (Trade name Double-sided paper adhesion tape, Kokuyo Co., Ltd.) to serve both as the drug permeability control membrane and the adhesive layer. This gave a reservoir-type transdermal preparation.

[Comparative Example 1]

[0027]

To 0.2 parts by weight of KRP-197, 0.1 parts by weight of gentamicin sulfate and 9.7 parts by weight of water were added and the components were dispersed to obtain a sample solution for evaluating the skin permeability of KRP-197 alone.

[0028]

<Test Example 1> (in vitro skin permeability test)

Excisions of shaved abdominal skin of male hairless rats (body weight = 229.7 to 328.1g) were each mounted on a horizontal diffusion cell (effective diffusion area = 0.95cm$^2$, cell volume = 2.5mL). As depicted in Fig. 3(a), each of the single adhesive layer-type transdermal preparations of

Examples 1 through 4 was applied to the stratum corneum of the shaved abdominal skin. The applied area was approximately 0.95$cm^2$. In Example 5, the KRP-197 suspension was placed in the cell on the stratum corneum side, and the double-sided tape to serve as the drug permeability control membrane and the adhesive layer was applied to the stratum corneum of the shaved abdominal skin, as depicted in Fig. 3(b). In Comparative Example 1, the sample solution for evaluating the skin permeability of KRP-197 alone was placed in the cell on the stratum corneum side, as depicted in Fig. 3(c). In each of Examples 1 through 5 and Comparative Example 1, phosphate buffer solution (pH 6.8) containing 1% gentamicin sulfate was placed in the cell on the dermis side. The phosphate buffer solution (pH 6.8) containing 1% gentamicin sulfate placed in the cell on the dermis side was sampled at intervals and each sample was analyzed by HPLC for the amount of KRP-197. The results of the analysis were used to plot the cumulative amounts of KRP-197 that had permeated through the skin. The rate of skin permeation was then determined from the slope of the plot. The results are shown in Table 1.

[0029]

[Table 1]

| Skin permeation rate (μg/hour/cm$^2$) | |
|---|---|
| Example 1 | 2.76 |
| Example 2 | 1.48 |
| Example 3 | 1.90 |
| Example 4 | 1.30 |
| Example 5 | 6.91 |
| Comparative Example 1 | 0.58 |

[0030]

As can be seen from the results of Table 1, the low skin permeability of KRP-197 (Comparative Example 1) was improved in each of Examples. Of the single adhesive layer-type transdermal preparations tested, the preparation of Example 1, which used styrene-isobutylene-styrene block copolymer, ultra-pale rosin ester, and isopropyl myristate in the base of the adhesive layer, exhibited the highest skin permeability of KRP-197. The rate of skin permeation of Example 1 was about five times higher than that of Comparative Example 1. The reservoir-type transdermal preparation of Example 5, in which L-menthol, ethanol (99.5) and water were used to form the base of the reservoir content and a double-sided tape was used to serve both as the adhesive layer and the drug permeability control membrane, showed a skin permeation rate about 12 times higher than that of Comparative Example 1.

[0031]

<Test Example 2> (in vivo skin application test)

The abdominal skin of male hairless rats (body weight = 202.9 to 252.3g) was shaved by an electric razor. A piece of the single adhesive layer-type transdermal preparation of

Example 1 or the reservoir-type transdermal preparation of Example 6, prepared based on the results of in vitro skin permeability test (Example 5), was applied to each rat in the shaved abdominal skin (Example 1 was applied over an about $3cm^2$ area, Example 6 over an about $9cm^2$ area). The preparations were secured by a strip of commercial surgical tape to prevent their peeling during the test. Blood samples were collected from subclavian vein at intervals and serum was separated. The serum concentrations of KRP-197 were determined by LC-MS/MS analysis. The results are shown in Fig. 4.

[0032]

As can be seen from Fig. 4, the single adhesive layer-type transdermal preparation of Example 1 and the reservoir-type transdermal preparation of Example 6 each showed sustained release of KRP-197.

[0033]

<Test Example 3> (Evaluation of primary skin irritation by Draize method)

Male rabbits (body weight = 2.90 to 2.96kg) were used. On the day before (24 hours before) the application of the preparations of Examples 1 and 6, the dorsal skin of each animal was shaved with electric hair clippers and an electric razor to form four application sites. Two of the four application sites were directly used as "normal skin" and the other two were scratched in the stratum corneum with a syringe

needle (to a depth that does not cause bleeding) and used as "damaged skin." The preparation of Example 1 was applied to one of the normal skin sites and one of the damaged skin sites and the preparation of Example 6 was applied to the other of the normal skin sites and the other of the damaged skin sites (Example 1 was applied over an about $3cm^2$ area, Example 6 over an about $9cm^2$ area). The preparations were each secured by a strip of adhesive bandage (Nichiban). The preparations were removed after 48 hours and the skin conditions were evaluated immediately after the removal and after 24 and 48 hours according to the Draize's criteria shown in Table 2.

[0034]

[Table 2]

| | |
|---|---|
| A. Erythema and eschar formation | |
| No erythema | 0 |
| Very slight erythema (barely perceptible) | 1 |
| Well-defined erythema | 2 |
| Moderate to severe erythema | 3 |
| Severe erythema (beet redness) and slight eschar formation | 4 |
| B. Edema formation | |
| No edema | 0 |
| Very slight edema (barelyperceptible ) | 1 |
| Slight edema (edges of area well defined by raising ) | 2 |
| Moderate edema (raised approx. 1mm) | 3 |
| Severe edema (raised more than 1mm and extending beyond area of exposure ) | 4 |

[0035]

The scores of the normal skin sites and the damaged skin sites were individually added and the totals were divided by 6 to obtain primary skin irritation indices. The safety classification was as follows: a preparation with a primary

skin irritation index of 0 to 2 was rated as a weak irritant; a preparation with a primary skin irritation index of 3 to 5 was rated as a moderate irritant; and a preparation with a primary skin irritation index of 6 or higher was rated as a strong irritant. The results are shown in Table 3.

[0036]

[Table 3]

| Test Examples | Classification | Scores | | | Primary skin irritation index | Safety class |
|---|---|---|---|---|---|---|
| | | 0 hr | 24 hrs | 48 hrs | | |
| Example 1 | Normal skin | 1.33 | 1 | 0.67 | 0.89 | Mild |
| | Damaged skin | 1 | 1 | 0.33 | | |
| Example 6 | Normal skin | 1 | 1 | 1 | 1.06 | Mild |
| | Damaged skin | 1.33 | 1 | 1 | | |

[0037]

As can be seen from Table 3, the single adhesive layer-type transdermal preparation of Example 1 and the reservoir-type transdermal preparation of Example 6 were each rated as a weak irritant and thus posed no serious irritation problems.

[INDUSTRIAL APPLICABILITY]

[0038]

According to the present invention, there is provided a transdermal preparation for treating increased urinary frequency and urinary incontinence that causes less skin irritancy and ensures efficient and sustained skin absorption of KRP-197 used as treatment for increased urinary frequency and urinary incontinence, which otherwise is hardly absorbed

through the skin. The preparation of the present invention circumvents the problem of solid oral preparations (e.g., tablets): the solid oral preparations are not suitable for administering drugs to children and aged people who have a low ability to maintain drug effect and swallow. The preparation of the present invention also circumvents the problems associated with commonly used non-oral preparations (e.g., injections and external preparations), such as follows: non-oral preparations may accompany pain; drugs cannot be eliminated once administered by non-oral preparations; non-oral preparations are difficult to use at home; and non-oral preparations, generally applied by patients themselves or their caretakers , result in poorly controlled drug delivery or dosage, leading to a reduced chance of proper drug use. These advantages should make the preparation of the present invention widely accepted by patients of varying ages, their caretakers, and medical personnels.

[BRIEF DESCRIPTION OF THE DRAWINGS]

[0039]

[Fig. 1] One example of cross-sectional view of a single adhesive layer-type transdermal preparation

[Fig. 2] One example of cross-sectional view of a reservoir-type transdermal preparation

[Fig. 3] A diagram of KRP-197 preparations used in an *in vitro* skin permeability test, where (a) shows a single

adhesive layer-type transdermal preparation used in Examples 1 through 4, (b) shows a preparation used in Example 5, and (c) shows a preparation used in Comparative Example 1.

[Fig. 4] The serum concentration profiles of KRP-197 in male hairless rats applied preparations of Examples 1 and 6

[INDICATION OF REFERENCE NUMERALS]

[0040]

1. Bucking
2. adhesive layer
3. peelable liner
4. Drug reservoir
5. adhesive layer (also serves as a membrane to control the permeability of drug)
6. single adhesive layer-type transdermal preparation
7. shaved abdominal skin of male hairless rat
8. KRP-197 dispersion in a cell on the stratum corneum side
9. drug permeability control membrane
10. sample solution for skin permeability test placed in a cell on the stratum corneum side. The solution contains KRP-197 alone.
11. PBS (pH 6.8) containing 1% gentamicin sulfate placed in a cell on the dermic layer side.

[Title of Document] ABSTRACT

[SUMMARY]

[OBJECT]

A transdermal preparation for treating increased urinary frequency and urinary incontinence is provided, which ensures stable and effective absorption of 4-(2-methyl-1-imidazolyl)-2,2-diphenylbutylamide (KRP-197) which has a low skin absorption and a bladder-selective anticholinergic effect, into body through the skin and providing sustained pharmacological effect with less skin irritancy.

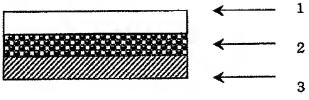
[Solving means]

A composition comprising KRP-197 and an external preparation base is deposited and dried onto a structural body or a small pool of the composition is deposited on the structural body to obtain a single adhesive layer-type transdermal preparation or a reservoir-type transdermal preparation. These preparations can ensure high permeation of KRP-197 through the skin and sustained absorption of KRP-197 into body while causing decreased skin irritancy.

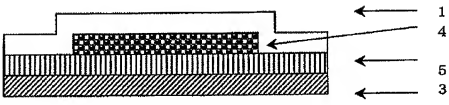
[Selected Drawing] None

[Title of Document] Drawings

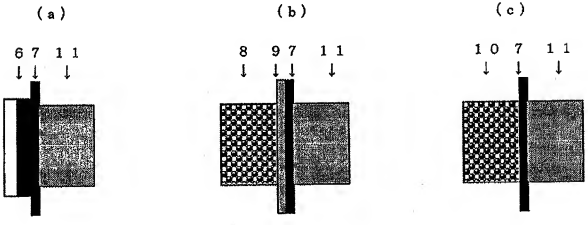
[FIG.1]




[FIG.2]




[FIG.3]




[FIG.4]